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- Published:
— with international search report (Art. 21(3))

[Continued on next page]

(54) Title: PATHWAYS CHARACTERIZATION OF CELLS

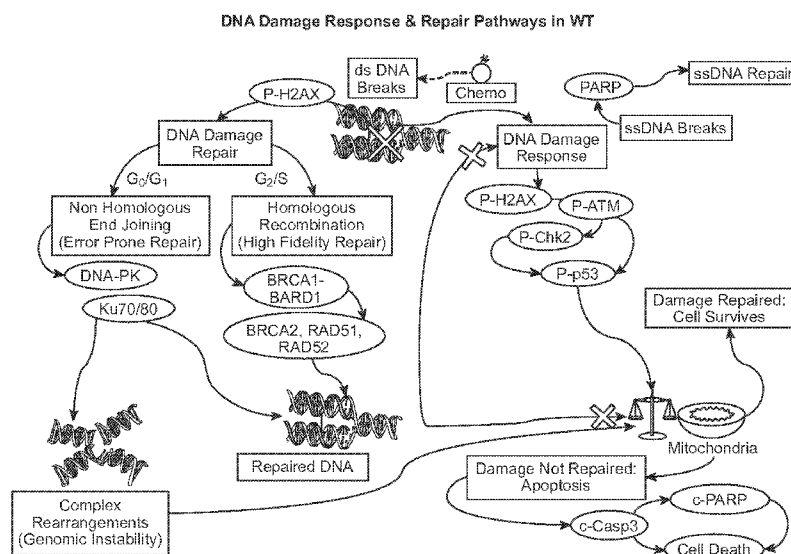


FIG. 2

(57) Abstract: The present invention provides methods, compositions and kits for the characterization of cellular pathways in cells containing genetic alterations.



(88) Date of publication of the international search report:

2 April 2015

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US13/45273

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12Q 1/68; G01N 33/566 (2013.01)

USPC - 506/9; 435/6.1, 6.14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): C12Q 1/68; C40B 30/40; G01N 27/26, 33/53, 33/559, 33/566 (2013.01)

USPC: 506/9; 204/456; 435/6.1, 6.14, 6.19, 7.1, 7.92

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; Google Patent; Pubmed; ProQuest; classify, diagnose, prognosis, cancer, predict, 'DNA damage' apoptosis, 'inducing agent', condition, 'cell population', activatable

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/156654 A2 (CESANO, A et al.) December 15, 2011; Claims 1-5, 12, 17-57	1, 2, 3, 4/1, 4/2, 4/3, 5/4/1, 5/4/2, 5/4/3, 12, 17-57
A	ROSEN, J et al. Distinct Patterns of DNA Damage Response and Apoptosis Correlate with Jak/Stat and PI3Kinase Response Profiles in Human Acute Myelogenous Leukemia. PLoS One. 25 August 2010, Vol. 5, No. 8: e12405, pp 1-13. DOI:10.1371/journal.pone.0012405.	1, 2, 3, 4/1, 4/2, 4/3, 5/4/1, 5/4/2, 5/4/3, 12, 17-57
A	O'CONNER, P et al. Characterization of the p53 Tumor Suppressor Pathway in Cell Lines of the National Cancer Institute Anticancer Drug Screen and Correlations with the Growth-Inhibitory Potency of 123 Anticancer Agents. Cancer Research. 01 October 1997, Vol. 57, pp 4285-4300.	1, 2, 3, 4/1, 4/2, 4/3, 5/4/1, 5/4/2, 5/4/3, 12, 17-57

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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10 JAN 2014

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6-11, 13-16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-Please See Supplemental Page-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Group I: Claims 1-5, 12, 17-57

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

-***-Continuation of Box No. III - Observations where unity of invention is lacking:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-5, 12 and 17-57 are directed toward a method of classification, diagnosis, prognosis and/or prediction of an outcome of a condition in an individual, said method comprising: a) contacting a cell population from said individual with a DNA damage or apoptosis inducing agent, wherein said cell population comprises a genetic and/or epigenetic alteration, wherein said alteration is associated with the development of said condition; b) characterizing a plurality of DNA damage repair pathways in one or more cells from said cell population by determining an activation level of at least one activatable element within said plurality of DNA damage repair pathways; c) determining whether said plurality of DNA damage pathways are functional in said individual based on the activation levels of said activatable elements; and d) making a decision regarding classification, diagnosis, prognosis and/or prediction of an outcome of said condition in said individual, wherein said decision is based on said determination on step (c); and a method of classification, diagnosis, prognosis and/or prediction of an outcome of a condition in an individual, said method comprising: a) contacting a cell population from said individual with a DNA damage apoptosis inducing agent, wherein said cell population comprises a genetic and/or epigenetic alteration, wherein said alteration is associated with the development of said condition, and wherein said cell population is not associated and/or is not causative of said condition; b) determining an activation level of at least one activatable element within a DNA damage pathway, an apoptosis pathway, and/or a cell cycle pathway in one or more cells from said cell population; and c) making a decision regarding classification, diagnosis, prognosis and/or prediction of an outcome of said condition in said individual, wherein said decision is based on said activation levels of said at least one activatable element within said DNA damage pathway, an apoptosis pathway, and/or a cell cycle pathway.

Group II: Claims 58-80 are directed toward a method of determining a signaling phenotype of a cell population, wherein said cell population comprises a genetic/epigenetic alteration of interest, said method comprising: a) subjecting said cell population comprising said genetic alteration to a plurality of modulators in separate cultures; b) characterizing at least one pathway in said cell population from separate plurality of cultures by determining an activation level of at least one activatable element within said at least one pathway; c) creating a response panel for said comprising said characterization of said at least one pathway from said separate cultures; and d) determining a signaling phenotype, wherein said signaling phenotype is based on said response panel.

Group III: Claims 81-101 are directed toward a method for detecting p53 levels in a cell population, said method comprising: a) subjecting said cell population to a modulator; b) contacting said cell population with a binding element specific for p53; and c) using flow cytometry to detect presence or absence of binding of said binding element to p53, wherein the presence or absence of binding of said binding element is indicative of the p53 levels in said population.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include a method of classification, diagnosis, prognosis and/or prediction of an outcome of a condition in an individual, said method comprising: a) contacting a cell population from said individual with a DNA damage or apoptosis inducing agent, wherein said cell population comprises a genetic and/or epigenetic alteration, wherein said alteration is associated with the development of said condition; b) characterizing a plurality of DNA damage repair pathways in one or more cells from said cell population by determining an activation level of at least one activatable element within said plurality of DNA damage repair pathways; c) determining whether said plurality of DNA damage pathways are functional in said individual based on the activation levels of said activatable elements; and d) making a decision regarding classification, diagnosis, prognosis and/or prediction of an outcome of said condition in said individual, wherein said decision is based on said determination on step (c); and a method of classification, diagnosis, prognosis and/or prediction of an outcome of a condition in an individual, said method comprising: a) contacting a cell population from said individual with a DNA damage apoptosis inducing agent, wherein said cell population comprises a genetic and/or epigenetic alteration, wherein said alteration is associated with the development of said condition, and wherein said cell population is not associated and/or is not causative of said condition; b) determining an activation level of at least one activatable element within a DNA damage pathway, an apoptosis pathway, and/or a cell cycle pathway in one or more cells from said cell population; and c) making a decision regarding classification, diagnosis, prognosis and/or prediction of an outcome of said condition in said individual, wherein said decision is based on said activation levels of said at least one activatable element within said DNA damage pathway, an apoptosis pathway, and/or a cell cycle pathway, which are not present in Group II, Group II having special technical features including a method of determining a signaling phenotype of a cell population, wherein said cell population comprises a genetic/epigenetic alteration of interest, said method comprising: a) subjecting said cell population comprising said genetic alteration to a plurality of modulators in separate cultures; b) characterizing at least one pathway in said cell population from separate plurality of cultures by determining an activation level of at least one activatable element within said at least one pathway; c) creating a response panel for said comprising said characterization of said at least one pathway from said separate cultures; and d) determining a signaling phenotype, wherein said signaling phenotype is based on said response panel, which are not present in Group III, Group III having special technical features including a method for detecting p53 levels in a cell population, said method comprising: a) subjecting said cell population to a modulator; b) contacting said cell population with a binding element specific for p53; and c) using flow cytometry to detect presence or absence of binding of said binding element to p53, wherein the presence or absence of binding of said binding element is indicative of the p53 levels in said population.

-***-Continued Within the Next Supplemental Box-***-

-Continued from Previous Supplemental Box-

Groups I-III share the technical features including a cell population and subjecting a cell population to a modulator; a determination or classification; a cell population comprising a genetic/epigenetic alteration of interest; at least one pathway, determining an activation level of at least one activatable element within said at least one pathway; a method of classification, diagnosis, prognosis and/or prediction of an outcome of a condition in an individual, said method comprising: a) contacting a cell population from said individual with a DNA damage or apoptosis inducing agent, wherein said cell population comprises a genetic and/or epigenetic alteration, wherein said alteration is associated with the development of said condition, and making a decision regarding classification, diagnosis, prognosis and/or prediction of an outcome of said condition in said individual.

However, these shared technical features are previously disclosed by WO 2011/156654 A2 to Cesano, et al. (hereinafter 'Cesano'). Cesano discloses a cell population (cell population; paragraph [0009]) and subjecting a cell population to a modulator (subjecting a cell population to a modulator; paragraph [0011]), a determination (determination; paragraph [0011]) or classification (classification; paragraph [0009]), a cell population comprising a genetic/epigenetic alteration of interest (a cell population comprising a genetic/epigenetic alteration of interest; paragraph [0009]), at least one pathway (a DNA damage repair pathway (at least one pathway); paragraph [0009]), determining an activation level of at least one activatable element within said at least one pathway (determining an activation level of at least one activatable element within said at least one pathway; paragraph [0009]), a method of classification, diagnosis, prognosis and/or prediction of an outcome of a condition in an individual (a method of classification, diagnosis, prognosis and/or prediction of an outcome of a condition in an individual; paragraph [0009]), said method comprising: a) contacting a cell population from said individual with a DNA damage or apoptosis inducing agent (said method comprising: a) contacting a cell population from said individual with a DNA damage or apoptosis inducing agent; paragraph [0009]), wherein said cell population comprises a genetic and/or epigenetic alteration (wherein said cell population comprises a genetic and/or epigenetic alteration; paragraph [0009]), wherein said alteration is associated with the development of said condition (wherein said alteration is associated with the development of said condition; paragraph [0009]), and making a decision regarding classification, diagnosis, prognosis and/or prediction of an outcome of said condition in said individual (making a decision regarding classification, diagnosis, prognosis and/or prediction of an outcome of said condition in said individual; paragraph [0009]).

Since none of the special technical features of the Groups I-III inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Cesano reference, unity of invention is lacking.